Docket No.: 273012011300
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ronald E. BOCH et al.

Application No.: 09/833,406 Confirmation No.: 3418

Filed: April 11, 2001 Art Unit: 1615

For: DRUG DELIVERY SYSTEM FOR HYDROPHOBIC DRUGS Examiner: G. Kishore

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby appeal from the final rejection of claims 21, 23-29, 31, 41, and 46-57 mailed March 25, 2004. A Notice of Appeal was filed along with a Petition for an Extension of Time on September 27, 2004 (September 25th being a Saturday) and was received in the Office on September 27, 2004. Filed herewith is a Petition and fee for a four month extension of time. Accordingly, this Brief is timely filed (March 27th being a Sunday). Appellants respectfully request that the rejection be reversed.

In accordance with 37 C.F.R. § 41.37(a), this Brief is accompanied by the required fee. The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

QLT, Inc.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

Appellant are aware of no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 22 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 1-20, 22, 30, 32-40, 42-45

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 21, 23-29, 31, 41, 46-57

4. Claims allowed: None

5. Claims rejected: 21, 23-29, 31, 41, 46-57

C. Claims On Appeal

The claims on appeal are claims 21, 23-29, 31, 41, 46-57.

IV. STATUS OF AMENDMENTS

Applicants filed an Amendment After Final Rejection on September 27, 2004 which included amendments to claims 21 and 41. No response to the Amendment After Final Rejection was received from the Office. No indication in PAIR was found as to whether or not the claim amendments were entered. A voice message was left for the Examiner on March 25, 2005 requesting the status of the amendment but no answer was received in time for this filing.

Accordingly, since Appellants do not know if the amendments filed September 27, 2004 were entered, two sets of claims are herein provided in Appendices A and B. The claims enclosed herein as Appendix A do not incorporate either the amendments to claims 21 and 41, as indicated in the September 27, 2004 paper filed. The claims in Appendix B do incorporate the amendments indicated in the paper filed on September 27, 2004.

V. SUMMARY OF CLAIMED SUBJECT MATTER

At the time of filing, the art was in search of suitable pharmaceutical formulations for hydrophobic polypyrrolic macrocyle based photosensitizers that could be filter-sterilized and freeze-dried, and could also be rapidly reconstituted in an aqueous medium prior to administration, while retaining a small particle size after rehydration. Appellants discovered a phospholipid composition into which hydrophobic photosensitizers may be incorporated that would meet these needs. In particular, it was found that the presence of at least some unsaturated lipid in the composition was essential for a stable, robust product that would survive the lyophilization process intact.

The present invention provides compositions comprising hydro-monobenzo-porphyrin photosensitizers which survive lyophilization and/or sterile filtration processes intact and thus, are suitable for pharmaceutical formulation. The invention of claims 21, 23-29, 31, and 46-51 is directed to compositions comprising micelles, where the micelles have an average diameter below about 100 nm and comprise saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer. The invention of claims 41, and 52-57 is directed to compositions *consisting essentially of* micelles, where the micelles have an average diameter below

about 100 nm and comprise saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are several rejections on appeal. The rejection applied to all claims 21, 23-29, 31, 41, and 46-57 to be reviewed on appeal is under 35 U.S.C. §103 as allegedly being obvious over Madden (U.S. Pat. No. 5,389,378) or Liu (U.S. Pat. No. 5,707,608) or Desai et al. (U.S. Pat. No. 6,074,666, hereinafter "Desai"). The rejection applied to all claims 21, 23-29, 31, 41, and 46-57 to be reviewed on appeal is under 35 U.S.C. §103 as allegedly being obvious over Madden or Liu or Desai in view of either Lentini (U.S. Pat. No. 5,885,557) or Young (U.S. Pat. No. 6,375,930) in further combination with Wan (U.S. Pat. No. 5,329,029).

VII. ARGUMENT

It is believed that the appeal should be resolved in favor of Appellants and the rejection of claims 21, 23-29, 31, 41, and 46-57 withdrawn for the following reasons:

Claims 21, 23-29, 31, 41, and 46-57 over Madden or Lui or Desai

A *prima facie* case of obviousness requires the satisfaction of three requirements. First, as in this case each reference is cited as a single, non-anticipatory document, the reference or art must suggest all of the claim limitations. Second, the reference must provide a suggestion or motivation to modify the teachings either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. Third, the reference must provide a reasonable expectation of success. *Manual of Patent Examination Procedure* (hereinafter "MPEP") § 2143.

More specifically, the obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Critical elements of the invention as a whole which clearly

distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Any disclosure teaching away from the claimed invention also must be considered in the obviousness analysis. MPEP § 2142.01. The fact that a disclosure can be modified is insufficient to establish *prima facie* obviousness in the absence of a suggestion or motivation to make such a modification. *Id.* Simply stated, the suggestion or motivation to modify a reference must be found in the prior art.

Appellants respectfully submit that a *prima facie* case for obviousness has not been established over Madden or Liu or Desai. The claimed invention is directed to a micelle composition in which the micelles in the composition have an average diameter below about 100 nm. The claimed micelles comprise saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer. Therefore, a *prima facie* case of obviousness requires that the cited reference or the art suggest a micelle composition in which the micelles in the composition have an average diameter below about 100 nm. Madden or Liu or Desai or the general knowledge of the art must provide a motivation to modify the teachings therein to result in the claimed compositions and must provide a reasonable expectation of success in modifying the teachings therein. For the reasons discussed below, each of the cited references fails to fulfill these requirements for *prima facie* obviousness.

Micelles refer to microaggregates with the hydrophobic (lipophilic) "tail" portion of the phospholipids generally oriented toward the interior of the micelle. Liposomes refer to microaggregates comprising at least one phospholipid bilayer, composed of two lipid monolayers having a hydrophobic "tail" region and a hydrophilic "head" region. Given the bilayer structure, a significant portion (up to about half) of the phospholipids will have their hydrophobic (lipophilic) portion generally oriented away from the center of the liposome. The average diameters of liposomes are larger than that of micelles. The specification describes processes and production conditions, including high energy processing, that result in the formation of micelles in otherwise liposome forming combinations of phospholipids and hydrophobic agents. Specification, for example, pages 44-48.

Madden, Lui and Desai each describes liposomal compositions and, as the Examiner admits, Madden, Lui and Desai all lack explicit teachings of micelle compositions. The Examiner states, however, that Madden, Lui and Desai "teach high energy processing steps" and that it would be obvious to the skilled artisan that the compositions in the references "would also contain micelles besides liposomes." Final Office Action, dated March 25, 2004, pages 4-5. The Examiner appears to be confusing obviousness with inherent anticipation. Appellants respectfully disagree both with this characterization of the teachings of cited references and with the assertions of obviousness regarding the claimed invention.

Since inherency is being relied upon for this rejection, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI, 1990) (emphasis in original). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' " Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); M.P.E.P. §2112.

Since the Examiner is saying that these compositions inherently include micelles as claimed, he must show that this is indeed the case. This showing, however, has not been provided nor has the Examiner provided basis that this position supports the obviousness rejection. Appellants note that the previously made anticipation rejections based on each of the same references were withdrawn in the March 25, 2004 Final Office Action.

The Examiner also asserts that "if formation of micelles were preferred, it would have been obvious to subject the phospholipid preparations to high energy processing steps till the formulations contain only micelles of desired sizes." Final Office Action, dated March 25, 2004, page 3. However, this statement does not support an obviousness rejection. To support this rejection, the Office must show why an artisan would prefer micelles. Not only do none of the

references show that micelles as claimed are produced by the process methods used, none of the cited references suggest that micelles as claimed should be prepared.

Madden does not teach or suggest the use of a high energy process for the preparation of liposomes but rather teaches use of an extrusion process to generate appropriate sized liposomes "ranging from about 100 to about 120 nm in diameter." Madden, col. 6, lines 36-59, and col. 12, lines 27-60. As noted in the paragraph bridging pages 35 and 36 of the present specification, the extrusion process does not produce micelles of the present invention. Further, Madden does not provide any motivation or suggestion for the modification of the teachings therein to generate a micelle composition with an average diameter below about 100 nm.

Although Lui mentions the use of high energy processes for the preparation of liposomes, Liu describes only the production of liposomes and, in the Example section, reports only the production of liposomes larger than 150 nm in diameter. For example, the preparation process taught in Example 5 resulted in liposome particles which averaged in size between 150 and 300 nm (col. 19, lines 5-32). In fact, when microfluidization steps are used, Lui cautions that as the number of microfluidization passes is increased, "more of the hydrophobic hydro-monobenzoporphyrin photosensitizer molecules are squeezed out of the liposomes, increasing the tendency of the liposomes to aggregate into larger particles." Lui, col. 12, lines 7-11. In addition, Liu describes that hydro-monobenzo-porphyrin are not soluble in micellar solutions and states that such photosensitizers may be administered by using a liposome composition (col. 7, lines 32-42). Accordingly, Lui teaches away from the claimed invention. Thus, taken in its entirety, Lui does not provide any motivation or suggestion for the modification of the teachings therein to generate a micelle composition with an average diameter below about 100 nm.

Desai does not teach or suggest use of a high energy processing step for the preparation of liposomes. As shown in Table I, the liposome preparation process of Desai generates liposomes with mean particle size greater than 100 nm (132-189 nm). Thus, Desai does not teach or suggest micelle compositions as claimed nor a process required for the formation of micelles as taught in the present invention. Desai states that the liposomal formulation taught therein "provides liposomes of

sufficiently small and narrow particle size such that is can be manufactured without filtering to separate off larger particles or utilizing other mechanical methods of obtaining a narrow distribution of particle size." Desai, col. 6, line 65, to col. 7, line 2, emphasis added. Thus, Desai provides no motivation or suggestion for the modification of the teachings therein to incorporate a high energy processing step for the generation of a micelle composition with an average diameter below about 100 nm.

Finally, none of the cited references provides a reasonable expectation of success of the claimed invention. Since Madden nor Lui nor Desai provides any motivation or suggestion for the modification of the teachings therein to generate a micelle composition with an average diameter below about 100 nm and since Lui describes that the claimed photosensitizer is not soluble in micellar solutions, it is impossible for any of the cited references to convey a reasonable expectation of success.

Accordingly, Appellants respectfully submit that a *prima facie* case of obviousness has not been established in view of Madden, Lui, or Desai.

The Examiner was not persuaded by arguments regarding these references and states that Appellants "are using art known liposome method of preparation steps such as aseptic filtration of the composition through 0.22 micron filters or micro fluidizers, sonicators, high-shear mixers and homogenizers (pages 35, 38, 43 and 45) which are the same as the methods employed by Madden, Lui and Desai." Final Office Action, dated March 25, 2004, page 6. The instant specification teaches both methods for the preparation of liposome compositions and methods for the preparation of micelle compositions. The claimed invention is directed to a micelle composition with the micelles having an average diameter below about 100 nm. Appellants respectfully submit that the fact that the specification includes teaching of methods for the preparation of liposomes has no bearing on the Examiner's *prima facie* case of obviousness in view of the cited references.

Claims 21, 23-29, 31, 41, and 46-57 over Madden or Lui or Desai in view of either Lentini or Young in further combination with Wan

When references are combined to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Further, the references must provide a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.

As discussed above, the primary references of Madden or Lui or Desai do not teach or suggest micelle compositions as claimed and do not support a *prima facie* case of obviousness over the claimed invention.

Lentini mentions micelles along with liposomes and gels as formulations for use in sustained-release delivery of psoralen. However, Lentini does not teach or suggest micelle compositions with micelles having an average diameter below about 100 nm as claimed nor methods to produce micelle compositions as claimed. Wan makes the general statement that phospholipids are capable of forming micelles and bilayers in an aqueous medium at column 2, lines 3-5, but does not provide any teaching as to methods and conditions necessary for the production of micelles nor with regard to micelles having an average diameter below about 100 nm.

Thus, Lentini even in combination with Wan does not supply what is missing from the primary references, Madden, Liu or Desai. The combinations of Madden or Liu or Desai and the secondary references do not provide any suggestion or motivation to modify the teachings therein to arrive at the claimed invention and, thus, do not render the claimed invention obvious. In addition, since none of these references, alone or in combined, teaches or suggests methods to produce micelles comprising saturated and unsaturated phospholipids and one of more hydro-monobenzo-porphyrin photosensitizer in which the micelles have an average diameter below about 100 nm, the

references do not provide a reasonable expectation of success of the claimed invention. Thus, a *prima facie* case of obviousness has not been established for the cited references.

Young describes micelles containing texaphyrin-lipophilic molecule conjugates but is silent with regard to formation of micelles that contain hydro-monobenzo-porphyrin photosensitizer as claimed. Although texaphyrin and hydro-monobenzo-porphyrin are both photosensitive compounds, the texaphyrin-lipophilic molecule conjugate of Young and the claimed hydro-monobenzo-porphyrin are different, distinct compounds. Wan makes the general statement that phospholipids are capable of forming micelles and bilayers in an aqueous medium but does not provide any teaching as to methods and conditions necessary for the production of micelles generally nor for the production of micelles of having an average diameter below about 100 nm. The Examiner states that "it is unclear whether [Young] specifically advocates [phospholipid] use in the micelle formation" but goes on to assert that the combination of Young, Wan and the primary references makes obvious the claimed invention. Final Office Action, dated March 25, 2004, page 5. Appellants respectfully disagree with this assertion.

The Examiner states that "Young shows the ability of phospholipid micelles to encapsulate active agents and this ability of micelles to encapsulate <u>any agent will be the same</u> and applicant has not shown that to be otherwise." Final Office Action, dated March 25, 2004, page 7, emphasis added. Notably, Young teaches that conjugation of the lipophilic molecule to the texaphyrin is an important aspect for vesicle loading success of the compound and that attempted loading with the texaphyrin alone was not successful. Young, col. 10, lines 33-36. Thus, contrary to the Examiner's assertion, Young indicates that active agent encapsulation is <u>not</u> necessarily the same of <u>any agent</u>, since texaphyrin conjugates are incorporated but texaphyrin itself is not. Thus, the teaching of Young does not provide an expectation of success for the claimed invention. Further, this teaching of Young together with Lui's discussion that hydro-monobenzo-porphyrin are <u>not</u> soluble in micellar solutions combines to move the skilled artisan even further from an expectation of success.

Thus, Appellants submit that Young and Wan do not supply what is missing from the primary references, Madden, Liu or Desai. The combinations of Madden or Liu or Desai and the secondary references do not provide any suggestion or motivation to modify the teachings therein to arrive at the claimed invention and, thus, do not render the claimed invention obvious. In addition, since none of these references, alone or in combination, teaches or suggests methods to produce micelles comprising saturated and unsaturated phospholipids and one of more hydro-monobenzo-porphyrin photosensitizer in which the micelles have an average diameter below about 100 nm, the references do not provide a reasonable expectation of success of the claimed invention.

Accordingly, a *prima facie* case of obviousness has not been established for the cited references.

For the reasons stated above, the rejections under 35 U.S.C. §103 may be properly withdrawn.

VIII. CLAIMS APPENDIX

A copy of the claims involved in the present appeal is attached hereto as Appendix A and Appendix B. As indicated above, the claims in Appendix A do not include the amendments filed by Applicants on September 27, 2004, and the claims in Appendix B do not include the amendments filed on September 27, 2004.

Dated: March 28, 2005

Respectfully submitted,

By 

Karen R. Zachow, Ph.D.
Registration No.: 46,332
MORRISON & FOERSTER LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
(858) 720-5191

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/833,406
(without amendments filed September 27, 2004)

Claims 1-20 (canceled)

Claim 21 (previously presented): A composition comprising micelles, said micelles comprising saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer

wherein said micelles have an average diameter below about 100 nm.

Claim 22 (canceled)

Claim 23 (previously presented): The composition of claim 21 wherein said one or more photosensitizer is BPD-MA, A-EA6, B-EA6 or a combination thereof.

Claim 24 (previously presented): The composition of claim 21 wherein one or more of said saturated and unsaturated phospholipids comprise a negatively charged headgroup.

Claim 25 (previously presented): The composition of claim 24 wherein said phospholipids comprise DOPG and DMPC.

Claim 26 (previously presented): The composition of claim 25 wherein the ratio of DOPG:DMPC is 40:60.

Claim 27 (previously presented): The composition of claim 21 wherein said micelles further comprise at least one antioxidant.

Claim 28 (previously presented): The composition of claim 27 wherein said at least one antioxidant is butylated hydroxytoluene (BHT) and/or ascorbyl palmitate (AP).

Claim 29 (previously presented): The composition of claim 21 wherein the ratio of phospholipids:photosensitizer is 8:1.

Claim 30 (canceled)

Claim 31 (previously presented): The composition of claim 23 wherein said photosensitizer is A-EA6 or B-EA6.

Claims 32-40 (canceled)

Claim 41 (previously presented): A composition consisting essentially of micelles, said micelles comprising saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer

wherein said micelles have an average diameter below about 100 nm.

Claims 42-45 (canceled)

Claim 46 (previously presented): The composition of claim 21 wherein said micelles have an average diameter below about 50 nm.

Claim 47 (previously presented): The composition of claim 46 wherein said micelles have an average diameter below about 30 nm.

Claim 48 (previously presented): The composition of claim 47 wherein said micelles have an average diameter below about 20 nm.

Claim 49 (previously presented): The composition of claim 21 wherein said unsaturated phospholipid is an egg phospholipid.

Claim 50 (previously presented): The composition of claim 21 wherein said unsaturated phospholipid is from a non-animal source.

Claim 51 (previously presented): The composition of claim 50 wherein said one or more photosensitizer is BPD-MA, A-EA6 or a combination thereof.

Claim 52 (previously presented): The composition of claim 41 wherein said micelles have an average diameter below about 50 nm.

Claim 53 (previously presented): The composition of claim 52 wherein said micelles have an average diameter below about 30 nm.

Claim 54 (previously presented): The composition of claim 53 wherein said micelles have an average diameter below about 20 nm.

Claim 55 (previously presented): The composition of claim 41 wherein said unsaturated phospholipid is an egg phospholipid.

Claim 56 (previously presented): The composition of claim 41 wherein said unsaturated phospholipid is from a non-animal source.

Claim 57 (previously presented): The composition of claim 56 wherein said one or more photosensitizer is BPD-MA, A-EA6 or a combination thereof.

APPENDIX B

Claims Involved in the Appeal of Application Serial No. 09/833,406
(with amendments filed September 27, 2004)

Claims 1-20 (canceled)

Claim 21 (currently amended): A composition comprising micelles, said micelles comprising saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer

wherein the micelles in the composition have an average diameter below about 100 nm.

Claim 22 (canceled)

Claim 23 (previously presented): The composition of claim 21 wherein said one or more photosensitizer is BPD-MA, A-EA6, B-EA6 or a combination thereof.

Claim 24 (previously presented): The composition of claim 21 wherein one or more of said saturated and unsaturated phospholipids comprise a negatively charged headgroup.

Claim 25 (previously presented): The composition of claim 24 wherein said phospholipids comprise DOPG and DMPC.

Claim 26 (previously presented): The composition of claim 25 wherein the ratio of DOPG:DMPC is 40:60.

Claim 27 (previously presented): The composition of claim 21 wherein said micelles further comprise at least one antioxidant.

Claim 28 (previously presented): The composition of claim 27 wherein said at least one antioxidant is butylated hydroxytoluene (BHT) and/or ascorbyl palmitate (AP).

Claim 29 (previously presented): The composition of claim 21 wherein the ratio of phospholipids:photosensitizer is 8:1.

Claim 30 (canceled)

Claim 31 (previously presented): The composition of claim 23 wherein said photosensitizer is A-EA6 or B-EA6.

Claims 32-40 (canceled)

Claim 41 (currently amended): A composition consisting essentially of micelles, said micelles comprising saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer

wherein the micelles in the composition have an average diameter below about 100 nm.

Claims 42-45 (canceled)

Claim 46 (previously presented): The composition of claim 21 wherein said micelles have an average diameter below about 50 nm.

Claim 47 (previously presented): The composition of claim 46 wherein said micelles have an average diameter below about 30 nm.

Claim 48 (previously presented): The composition of claim 47 wherein said micelles have an average diameter below about 20 nm.

Claim 49 (previously presented): The composition of claim 21 wherein said unsaturated phospholipid is an egg phospholipid.

Claim 50 (previously presented): The composition of claim 21 wherein said unsaturated phospholipid is from a non-animal source.

Claim 51 (previously presented): The composition of claim 50 wherein said one or more photosensitizer is BPD-MA, A-EA6 or a combination thereof.

Claim 52 (previously presented): The composition of claim 41 wherein said micelles have an average diameter below about 50 nm.

Claim 53 (previously presented): The composition of claim 52 wherein said micelles have an average diameter below about 30 nm.

Claim 54 (previously presented): The composition of claim 53 wherein said micelles have an average diameter below about 20 nm.

Claim 55 (previously presented): The composition of claim 41 wherein said unsaturated phospholipid is an egg phospholipid.

Claim 56 (previously presented): The composition of claim 41 wherein said unsaturated phospholipid is from a non-animal source.

Claim 57 (previously presented): The composition of claim 56 wherein said one or more photosensitizer is BPD-MA, A-EA6 or a combination thereof.